UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,498	10/27/2004	Hansjorg Reimann	DECLE96.001APC	4048

20995 7590 04/12/2007

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
HINES, JANA A	
ART UNIT	**PAPER NUMBER**
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	04/12/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 04/12/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
eOAPilot@kmob.com

Office Action Summary	Application No.	Applicant(s)	
	10/509,498	REIMANN ET AL.	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/28/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on September 28, 2004 was filed. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Specification

2. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

3. Claims 10-11 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 10 and 11 fail to further limit the vaccine composition and the kit. Neither claims adds any additional components to the vaccine composition or the kit, therefore appropriate clarification is required to overcome the objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunogenic composition suitable for administration to a vertebrate host, which comprises:(a) a polynucleotide vaccine component comprising a polynucleotide encoding a vaccine Hepatitis B surface antigen, such that introduction of polynucleotide into said vertebrate host results in expression of a biologically effective amount of said antigen so as to induce a prophylactic or therapeutic immune response;(b) a protein antigen vaccine component comprising a protein antigen selected from the group consisting of bovine serum albumin, hen egg lysozyme and Hepatitis B surface antigen; and (c) a mineral-based, negatively charged adjuvant, does not reasonably provide enablement for a vaccine composition suitable for administration to a vertebrate host, which comprises:(a) a polynucleotide vaccine component comprising at least one polynucleotide encoding at least one antigen, such that introduction of said formulation into said vertebrate host results in expression of a biologically effective amount of said antigen or antigens so as to induce a prophylactic or therapeutic immune response; (b) a protein antigen vaccine component comprising at least one protein antigen selected from the group consisting of model protein antigens

and vaccine protein antigens; and (c) a mineral-based, negatively charged adjuvant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. This is a scope of enablement rejection.

The specification teaches the mixing of a plasmid Hepatitis B surface antigen (HBsAg) DNA, a protein antigen encoding the same, aluminum phosphate and either bovine serum albumin (BSA) or hen egg lysozyme (HEL); see page 9 of the instant specification. The specification has failed to provide a structure for all of the polynucleotide vaccine components and protein antigen vaccine components encompassed by the claimed invention. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides and protein antigens broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative vaccine compositions. Since the nucleotide sequence determines its structural and functional properties, predictability of which changes can be tolerated and still retain similar activity requires a knowledge with regard to the nucleotides sequence, and the detailed knowledge of the ways in which the encoded protein's structure relates to function. However, the problem of the prediction of protein's structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein with respect thereto is extremely complex and outside of the realm of routine experimentation. It is not routine in the art to screen multiple

polynucleotides that encode at for a vaccine antigen, and protein antigen compositions with a reasonable expectation of success.

The claims and specification fail to disclose the specific type of vaccine components that should be administered. The specification shows that an antibody response was generated in mice, however it is well known that merely generating an immune response does not equate to providing protective immunity. The instant specification fails to provide any experiments that show that such vaccines would be effective in protecting a human or other vertebrate host against an undefined pathogen. The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity to an infection or disease induction. The vaccine art is highly unpredictable and the instant specification fails to provide any information that the recited vaccine would provide any immunity to a vertebrate host against any type of infection. There are still no immunological experiments provided to demonstrate that the claimed vaccines are capable of mounting an effective immune response. More importantly, there are no challenge experiments to demonstrate that a vertebrate host immunized with the claimed vaccine composition would be protected from any infection. There are no protocols provided which demonstrate which composition would be effective in immunization, nor are their protocols detailing the amount of vaccine composition needed to mount a sufficient immune response. There is no teaching as to what the most effective route of administration for the claimed vaccines. There is merely a general outline of vaccines that do not apply directly to the instant invention.

The ability to reasonably predict the capacity of a single immunogen to induce protective immunity from in vitro antibody reactivity studies is problematic. Ellis exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of the protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies" (page 572, second full paragraph). Unfortunately, the art is replete with instances where even well characterized antigens that induce an in vitro neutralizing antibody response fail to elicit in vivo protective immunity. See Boslego et al. wherein a single gonococcal pillin protein fails to elicit protective immunity even though a high level of serum antibody response is induced (page 212, bottom of column 2). Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful attenuated live or whole cell vaccine without the prior demonstration of vaccine efficacy.

Factors to be considered in determining whether undue experimentation is required are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims. Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting polynucleotides and protein antigens having claimed functional

features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use a polynucleotide vaccine component comprising at least one polynucleotide encoding at least one antigen, such that introduction of said formulation into said vertebrate host results in expression of a biologically effective amount of said antigen or antigens so as to induce a prophylactic or therapeutic immune response;(b) a protein antigen vaccine component comprising at least one protein antigen selected from the group consisting of model protein antigens and vaccine protein antigens; and (c) a mineral-based, negatively charged adjuvant in manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue. The Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the vaccine composition's activity is unpredictable and the experimentation left those skilled in the art is unnecessarily and improperly, extensive and undue. See Amgen Inc v Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Ex parte Forman, 230 U.S.P.Q. 546(Bd. Pat. App & Int).

This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of preventing any infection or disease. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict

if protective immunity has been induced. The specification fails to teach the identity a vaccine composition with the claimed characteristics. Furthermore, the specification fails to adequately disclose a description of the claimed vaccines, thus a skilled artisan would be required to de novo locate, identify and characterize the claimed vaccines. Accordingly, this would require undue experimentation given the fact that the specification is completely lacking in teachings. Thus, the art indicates that it would require undue experimentation to formulate and use a successful vaccine composition without the prior demonstration of vaccine efficacy.

5. Claims 1-11 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claim 1 recites the limitation "said formulation" in the claim. There is insufficient antecedent basis for this limitation in the claim. Appropriate clarification is required to overcome the rejection.

b) Claims 4 and are rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Acronyms like IEP and HBV must be spelled out when used for the first time in a chain of claims. Appropriate clarification is required to overcome the rejection.

c) Regarding claim 5, the phrase "i.e.," renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "i.e."), thereby

rendering the scope of the claim unascertainable. Appropriate clarification is required to overcome the rejection.

d) Claim 5 recites alternative limitations for the group of vaccine protein antigens which are improperly expressed. Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group recites members as being "selected from the group consisting of A, B and C". Another acceptable form recites "selected from 1, 2, 3, or 4." Applicant may correct this by amending the claim to recite the appropriate language.

e) Claim 9 provides for the use of a mineral-based, negatively charged adjuvant, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claim 9 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd. App. 1967) and

Clinical Products, Ltd. v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Appropriate clarification is required to overcome the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Dalemans et al., (WO 99/30733).

The claims are drawn to a vaccine composition suitable for administration to a vertebrate host, which comprises: (a) a polynucleotide vaccine component comprising at least one polynucleotide encoding at least one antigen, such that introduction of said formulation into said vertebrate host results in expression of a biologically effective amount of said antigen or antigens so as to induce a prophylactic or therapeutic immune response;(b) a protein antigen vaccine component comprising at least one protein antigen selected from the group consisting of model protein antigens and vaccine protein antigens; and (c) a mineral-based, negatively charged adjuvant. The dependant claims are drawn to specific adjuvants, model protein antigens, and vaccine protein antigens. The claims are also drawn to a kit comprising the vaccine composition and a method of using the adjuvant as a component in a combined DNA/protein based vaccine composition.

Dalemans et al., teach administration of combination DNA vaccines to mammals, such as man (page 3, lines 28-30). Dalemans et al., teach DNA vaccines by admixing two different compounds wherein the first compound comprises a polynucleotide (nucleic acid) such as DNA or RNA which-encodes a selected polypeptide that can stimulate protective immunity and the second compound comprises a polypeptide, which preferably is the same polypeptide (or substantially the same, i.e., having the same immunodominant epitope(s) encoded by the nucleic acid (page 5-6, lines 29-2). When nucleic acid such as DNA encoding the gene of interest is admixed with the corresponding polypeptide is administered to a mammal, a synergistic effect is observed wherein not only is the DNA vaccine capable of inducing an immune response in the presence of protein (polypeptide), but the presence of such protein (polypeptide) has been found to actually enhance the efficacy of the DNA vaccine (page 6, lines 6-11). Thus, one aspect of the present invention is a composition comprising a polynucleotide and polypeptide for enhancing an immune response wherein the polypeptide is adjuvanted (page 6, lines 11-14). Thus Dalemans et al., teach prior mixing of the polypeptide or protein antigen with the adjuvant.

The polynucleotide comprises DNA or RNA polynucleotide sequences coding for polypeptides that have useful therapeutic application, e.g., prophylactic or therapeutic vaccines (page 7, lines 14-16). Both expressible DNA and RNA can-be delivered to cells to form therein a polypeptide translation product wherein the encoded antigens are associated with infectious diseases caused by, for instance, all forms of Hepatitis and polio, (page 5, lines 17-22). Therefore Daleman et al., teach a polynucleotide vaccine

component comprising a polynucleotide encoding an antigen, such that introduction of said formulation into a vertebrate host results in expression of a biologically effective amount of said antigen so as to induce a prophylactic or therapeutic immune response. The protein antigen can be a polypeptide that also has a useful therapeutic application, e.g., as a prophylactic or therapeutic vaccine (page 6, lines 20-21). The vaccine composition is not limited to a particular polypeptide and can have the same immunodominant epitopes encoded by the nucleic acid (page 6, lines 21-22). Therefore Dalemans et al., that the polypeptide or protein antigen component can comprise an antigen a surface protein or an antigen derived from inactivated polio virus. Dalemans et al., teach the administration of a polynucleotide/polypeptide composition, should enhance the induction of immunity because the administration of one compound also both components to act during the same ongoing immune response (page 7, lines 25-29 and page 8, line 10).

The polynucleotide + polypeptide mixture (complex), when adjuvanted, are preferably adjuvanted with suitable adjuvants that include an aluminum salt such as aluminum hydroxide (alum), aluminum phosphate, but also can be a salt of calcium (page 18-25). Therefore, Dalemans et al., teach a mineral-based, negatively charged adjuvant that is an aluminum or calcium salt, such as aluminum hydroxide and aluminum phosphate. Also, Dalemans et al., teach a method of using the adjuvant as a component in a combined DNA/protein vaccine composition. Dalemans et al., teach that the vaccine formulation includes an adjuvant that encodes CpG sequences, wherein such CpG sequences, or motifs, are known in the art (page 10, lines 4-6). The art

teaches that palindromic CpG sequences have immunostimulatory activities and are instrumental in aiding DNA vaccine by providing an activation signal to antigen presenting cell. The instant specification at page 5, lines 12-15 define model protein antigens as a protein which is not derived from an infectious microorganism which may cause one or more diseases with the aim of eliciting a protective immune response towards the model protein itself. The CpG sequence meets the limitation of being a model protein antigen since CpG is not derived from an infectious microorganism which may cause one or more diseases and the protein does not elicit a protective immune response towards CpG. Therefore Dalemans et al., teach the inclusion of a model protein.

Dalemans et al., teach that the composition is packaged in a per unit dosage or unit dosage ampoules or multidose containers, in which the polynucleotides and polypeptides are packaged prior to use enclosing an amount of polynucleotide and polypeptide or solution containing a polynucleotide and polypeptide suitable for a pharmaceutically effective dosing (page 11, lines 2-30). Therefore teach a unit dose form for administration to a vertebrate recipient.

Therefore Dalemans et al, teach a vaccine composition for administration to a vertebrate or human host, which comprises: (a) a polynucleotide vaccine component comprising at least one polynucleotide encoding at least one antigen, such that introduction of said formulation into said vertebrate host results in expression of a biologically effective amount of said antigen or antigens so as to induce a prophylactic or therapeutic immune response;(b) a protein antigen vaccine component comprising at

least one protein antigen selected from the group consisting of model protein antigens such as CpG and vaccine protein antigens; and (c) a mineral-based, negatively charged adjuvant such as aluminum hydroxide or aluminum phosphate. Dalemans et al., also teach a kit comprising the vaccine composition in unit dosage form and a method of using the adjuvant as a component in the combined DNA/protein vaccine composition.

Prior Art

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. WO 97/28818 teaches novel vaccines comprising a nucleic acid encoding a first epitope and a peptide containing a second epitope and an aluminum adjuvant.

Conclusion

9. No claims allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Jeffery Siew, can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines
March 21, 2007

MARK NAVARRO
PRIMARY EXAMINER